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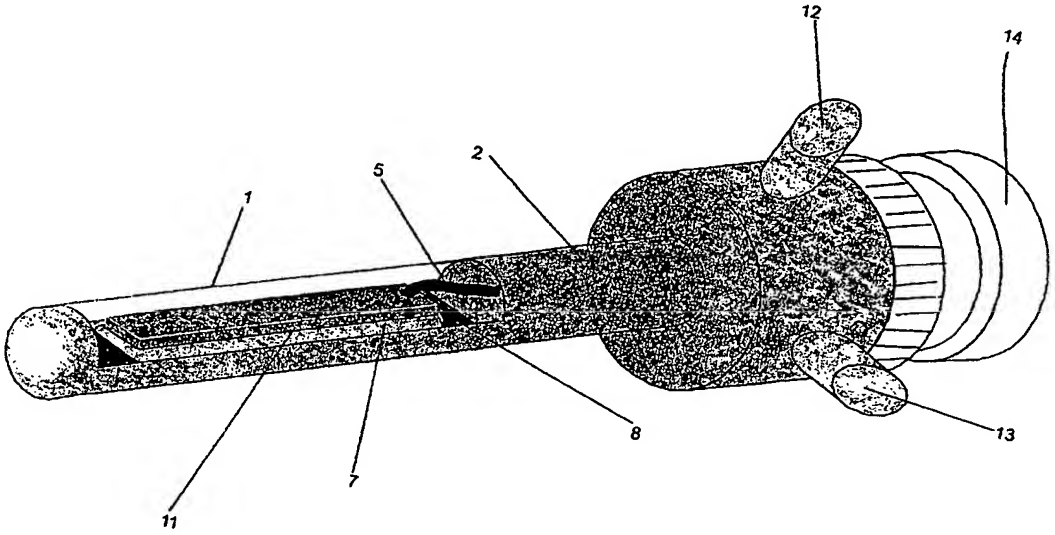
(54) Title: TECHNIQUE AND APPARATUS FOR ULTRASOUND THERAPY



(57) Abstract: The present invention is directed to an imaging compatible device which employs ultrasound energy for thermal therapy. Directionality of the thermal therapy is effected through transducer structure and rotational control of the device. The depth of thermal therapy can also be controlled through simultaneous modulation of the device's operating frequencies and ultrasonic power. The device comprises at least one transducer, in combination with at least one acoustic coupling layer, adapted to provide mutlifrequency operation, and located within a housing suitable for tissue insertion. The invention also provides methods of using the device for providing thermal therapy or for activating an/or enhancing the delivery of therapeutic agents.

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Title: Technique And Apparatus For Ultrasound Therapy

FIELD OF THE INVENTION

The present invention relates to the field of thermal therapy for treatment for various medical conditions, for example, tumors, and is concerned with ultrasound therapy, more particularly the devices and methods of use of such devices.

BACKGROUND OF THE INVENTION

Thermal therapy is a technique for the treatment of tumors in which heat is used to destroy cancerous tissue. It is a potential candidate for the treatment of solid, localized tumors in tissue. "Hyperthermia" refers to thermal therapies in which the target temperatures achieved in tissue are between 42 and 46°C. In this temperature region, the relationship between cell death, temperature and time is described by a thermal dose equation, and exposure times are typically between 30 and 60 minutes at 43-45°C (Dewey, 1994). Thermal coagulation refers to thermal therapies in which target temperatures achieved in tissue are between 55 and 90°C. The application of temperatures in excess of 55°C results in rapid destruction of tissue primarily through thermal coagulation. This higher temperature regime delivers sufficient energy to denature proteins and produces complete cell death in the treated region within a short time (seconds) (Thomsen, 1991).

The use of thermal coagulation for tissue destruction is predicated on effective guidance and monitoring of heat delivery. Medical imaging plays an integral role, providing important information about anatomy, temperature, and tissue viability during and after the delivery of heat. This information can be used to target heat delivery to specific locations, monitor the amount of heat delivered, and assess the biological damage incurred, thereby eliminating the need to expose the treatment site to visual assessment. Monitoring the spatial delivery of heat with magnetic resonance imaging (MR) can help avoid damage to critical structures and other normal tissue.

In interstitial thermal therapy, heat is produced by devices inserted directly into a target site within an organ. Potentially less invasive than conventional surgery, this approach can make possible the treatment of tumors in otherwise inaccessible locations. Several technologies have been employed for interstitial heating, including lasers, radio-frequency waves, and microwaves. These devices have been shown to be capable of generating temperature elevations sufficient for thermal coagulation of tissue. Some characteristics of these devices, however, limit their ability to treat large volumes or regions close to important anatomical structures. Temperatures which are too high (>90°C) close to the device surface can lead to undesirable physical effects such as charring or vaporization in tissue. Inadequate heating can occur at the target boundary due to rapid decreases in deposited power with increasing distance from the device. A common characteristic among existing interstitial devices is the shape of the spatial heating pattern, usually spherical or ellipsoidal. This property makes the treatment of asymmetrically shaped volumes of tissue difficult. The goal with interstitial thermal devices is to deliver a heating pattern which is as uniform as possible to the entire target volume of tissue, while avoiding excessive or inadequate heating.

The ability to generate rapid, localized temperature increases in tissue has led to the development of focused ultrasound as a method to treat tumors. Magnetic resonance (MR) imaging is well suited for use in conjunction with high intensity ultrasound as a means of treatment guidance and monitoring. MR-derived information can indicate beam position, tissue temperature, and can distinguish regions of thermal coagulation (McDannold et al., 1998; de Poorter et al., 1996; Chung et al., 1996). The feasibility of MRI-guided therapy with high intensity focused ultrasound has been demonstrated (Hynynen et al., 1996).

A thermal treatment requires the coagulation of all the tissue within the tumor volume (Malcolm and ter Haar, 1996). In the case of a focused beam from an external transducer, multiple small lesions are placed throughout the target volume. For complete tumor coagulation, lesions must

be closely spaced or overlapped, but gaps in coverage and unpredictable lesion formation can occur due to changes in the acoustic properties of heated tissue (Chen et al., 1997; Damianou et al., 1997).

A confounding factor, in the case of externally focused ultrasound, is the heating of intervening tissue in the nearfield of the acoustic beam (Damianou and Hynynen, 1993). In the extreme case, this can result in burning of the skin (Rivens et al., 1996). To overcome this problem, sonications are separated by sufficient time for intervening areas to cool down, usually 1-2 minutes (Fan and Hynynen, 1996). This approach can reduce damage to intervening layers of tissue but treatment times become unacceptably long (1-2 hours). Transducer systems have, thus, been designed to coagulate larger volumes per sonication in an effort to reduce treatment times (Fjield et al., 1997; Ebbini and Cain, 1988; Lizzi et al., 1996, McGough et al., 1994)

A different approach is to use interstitial ultrasound heating applicators designed for insertion into tissue under image guidance, which deposit energy directly within a targeted region. The delivery of ultrasound is localized to the tumor, and the problem of heating intervening tissue layers is avoided. Interstitial transducers have been developed for a variety of applications including cardiac ablation (Zimmer et al., 1995), prostate cancer (Deardorff et al., 1998), and gastrointestinal coagulation (Lafon et al., 1998).

Scanning an acoustic beam permits the energy concentrated in the acoustic field to be distributed over a volume. This can result in more uniform heating of a larger region of tissue. The effects of scanning an acoustic beam for hyperthermia (Hynynen et al., 1986; Moros et al., 1988), and more recently for high intensity thermal coagulation (Chen et al., 1997) have been studied. At acoustic intensities sufficient for tissue coagulation, scanning generated continuous regions of thermal damage in excised liver specimens (Chen et al., 1997). This scanning technique is unsuitable for external ultrasound therapy due to excess nearfield heating, but is potentially well advantageous for interstitial ultrasound heating.

The theoretical heating patterns of single element and linear array transducers has been investigated in a previous study by Chopra et al. (2000). These calculations indicated the differences in the heating patterns from the two transducer designs, and highlighted the importance of achieving a high output acoustic power. However, there is a continuing need for a heating device which is able to deliver a uniform heating pattern to a target volume of tissue.

SUMMARY OF THE INVENTION

The present invention comprises a multifrequency ultrasound heating applicator for thermal therapy of tissue. Preferably, an applicator according to the invention is compatible with imaging, more preferably MR imaging. Such an applicator is also preferably compatible with image-guided interstitial therapy, preferably of benign or malignant tissues. In its broad aspect the interstitial ultrasound applicator of the present invention is comprised of at least one transducer, each preferably planar, and one or more acoustic coupling layers which, in combination with the at least one of the of the at least one transducer, provide for multifrequency operation for optimal "control" of the depth of thermal coagulation.

In an embodiment of the present invention, an applicator has capability for varying the frequency and power of each transducer included therein thereby enabling the tissue temperature to be adjusted both radially and along the length of the applicator or catheter. This provides critical adjustability for accommodating irregular tumor geometry, heterogeneities of the tissue thermal properties, and dynamic changes in perfusion. In addition, the heat deposition pattern is not significantly dependent on the length of insertion or placement of the device with regard to the target or other devices in the implant.

Accordingly, the present invention provides a multifrequency ultrasonic device comprising a housing and at least one transducer provided in the housing. Each of the transducers have first and second opposed surfaces. The device further comprises at least one acoustic coupling layer

provided on at least one of the first and second surfaces of at least one of the transducers. The device further comprises an acoustic window for transmission of ultrasound energy generated by each transducer and means for delivering sufficient power to the transducers for generating ultrasonic energy to thermally coagulate tissue.

In another aspect, the present invention provides for a multifrequency ultrasonic device comprising a housing, at least one transducer provided in the housing with each transducer having first and second opposed surfaces and a plurality of acoustic coupling layers provided on at least one of the first and second surfaces of at least one of the transducers. The device further comprises an acoustic window for transmission of ultrasound energy generated by each transducer and means for providing power to the transducers.

In a further aspect, the present invention provides for a multifrequency ultrasonic device comprising a housing, at least one transducer provided in the housing with each transducer having first and second opposed surfaces and at least one acoustic coupling layer provided on at least one of the first and second surfaces of at least one of the transducers. The device further comprises an acoustic window for transmission of ultrasound energy generated by each transducer, means for providing power to the transducers and, a motor control system to provide rotational control of at least a portion of the housing that contains the transducers to isolate heating to parts of tissue.

In a further aspect, the present invention provides a method for ultrasonic thermal therapy of tissue. The method comprises:

a) determining a target tissue volume from images;

b) planning a route of insertion and a heating regime based on the images;

c) inserting a device following the route;

d) delivering ultrasonic energy from the device to the target tissue volume to produce a thermal lesion; and

e) assessing the thermal lesion with imaging.

In yet a further aspect, the present invention provides a method of delivering ultrasound for the purposes of activating a therapeutic agent in a target tissue volume to deliver therapy. The method comprises:

a) determining the target tissue volume from images;

b) planning a route of insertion and an activation regime based on the images;

c) inserting a device following the route;

d) delivering ultrasonic energy to activate the therapeutic agent; and,

e) assessing the efficacy of activation.

in yet a further alternative embodiment, the present invention provides a method for obtaining diagnostic information from a target tissue volume. The method comprises:

a) determining the target tissue volume from images;

b) planning a route of insertion based on the images;

c) inserting an ultrasonic device following the route; and,

d) obtaining ultrasonic diagnostic information from the target tissue volume.

Other features of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only. Various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

The following figures describe the nature of the proposed device, in order to clarify its design and application for thermal therapy:

Figure 1 is a flow diagram illustrating the method of image-guided interstitial coagulation of tumors.

Figure 2 is a three dimensional view of an embodiment of a heating applicator of the present invention.

Figure 3 is a transverse cross-section through the heating applicator of Figure 2 at the location of the transducer showing the mechanical and electrical structure and cooling supply.

Figure 4 is an axial cross-section through the heating applicator of Figure 2.

Figure 5 illustrates possible transducer configurations for a heating applicator of the present invention.

Figure 6 shows increased power transmission bandwidth available for transducers of the invention with multiple matching layers.

Figure 7 is a cross-sectional view of transducer according to the invention showing acoustic coupling layers.

Figure 8 is a graph of the theoretical transverse power distribution emitted from a transducer surface for 4, 6 and 8 MHz fields.

Figure 9 shows the predicted power transmission bandwidth for multilayer transducers with various configurations of acoustic coupling layers.

Figure 10 shows the calculated and measured power transmission band width for a transducer of the invention with a one 1/4λ high acoustic impedance layer.

Figure 11 shows the calculated and measured power transmission bandwidth for an interstitial transducer according to the invention with two 1/2λ high acoustic impedance layers.

Figures 12a, 12b and 12c show simplified diagrams of the transducer having layers at various orientations.

DETAILED DESCRIPTION OF THE INVENTION

As mentioned above, the present inventors have developed an ultrasound heating applicator for therapy of tissue. In addition an embodiment of an applicator of the invention is compatible with imaging.

As used herein, the expressions "heating applicator" and "applicator" mean the device used to conduct thermal therapy and which is the subject of the present specification.

As used herein, the expression "scan" means the energy from an applicator transmitted over a region of tissue as achieved through movement of an applicator of the invention, where the movement may include periods of no movement, combined with movement, or continuous movement.

As used herein, the expression "transducer" means one or more elements capable of emitting ultrasound.

As used herein, the term acoustic coupling layer(s) indicates one or more layers of material having acoustic impedance properties which, in combination with a transducer, provide for multifrequency operation of the device. In one instance, the acoustic coupling layers may be one or more acoustic matching layers having an acoustic impedance which is stepped down from the acoustic impedance of the transducer to the acoustic impedance of the tissue. In another instance, the acoustic coupling layers may be one or more high acoustic impedance layers which, in combination with a transducer, provide for multiple frequency operation of the device such that the transmission spectrum for the device comprises multiple narrowband peaks. In another instance, the acoustic coupling layers may be a combination of one or more acoustic matching layers and one or more high acoustic impedance layers which, in combination with a transducer, provide a device having a transmission spectrum comprising multiple narrowband peaks wherein each peak is wider than each narrowband peak obtained when only

high acoustic impedance layers are combined with a transducer. More than one transducer in combination with the acoustic coupling layers may also be used as described further below.

Heating Applicator

In its broad aspect a device according to the present invention is an interstitial ultrasound applicator comprised of a transducer with multiple acoustic coupling layers enabling operation at a range of frequencies for optimal control of the depth of thermal coagulation. In an embodiment, the range of frequencies may be delivered simultaneously from the same transducer or different frequencies may be delivered from different elements of a multi-element transducer. The transducer shape can be oval, planar, semi-circular, octagonal, hexagonal or any polygon or shape. According to one embodiment, the device is seated in a housing, preferably a tubular housing, more preferably the housing is rigid. A temperature control system is also available where the coolant is used to control the temperature of the transducer. Such use of the coolant may heat or cool the immediately adjacent tissue. Preferably, local temperature control is achieved by having water flowing across the surface of the device.

The transducer may be a single element, multi-element or a phased array transducer depending on the requirements on the accuracy and control over the spatial pattern of heating. The operating frequency range for these transducers is typically between 2 and 12 MHz, and between 10 and 60 W of electrical power is delivered to the device during heating. The generation of a conformal heating pattern is possible through rotational control of the applicator, and control over the radial and axial depth of thermal coagulation. These characteristics result in the ability to prescribe and deliver a three-dimensional pattern of thermal coagulation in tissue.

The heating applicator is designed to be used in conjunction with any type of imaging device including MRI, ultrasound, CT, or any device which is able to allow the imaging of an applicator of the invention, in other words, that makes the applicator visible. However, MR imaging is preferable.

MR imaging can be used to define the target tumor and surrounding anatomical structures, ultimately guiding the insertion path and approach of the device. Rapid imaging, accomplished with MRI and/or ultrasound can guide the device during insertion to ensure that correct placement is achieved. During the delivery of ultrasound to tissue, MR can non-invasively measure the temperature distribution in the region of tissue around the heating applicator to ensure that excessive heating is avoided close to the applicator, and adequate heating occurs at the treatment boundary. Finally, upon completion of treatment, MR images sensitive to thermal damage of tissue, such as T2-weighted and/or contrast-enhanced T1-weighted images can be acquired of the treatment volume to assess the extent of thermal coagulation.

The design of a preferred embodiment of an applicator according to the present invention is for the delivery of high intensity multifrequency ultrasound to a tumor. Temperatures exceeding 55°C are achieved in the tumor volume. To achieve such rapid heating, high power is preferably delivered to the ultrasound transducer, and according to one embodiment, water cooling is employed in order to remove any thermal losses. As will be appreciated by those skilled in the art, alternative means such as other cooling liquids, air or variety of gases, may be employed to remove such thermal losses. Since, in a preferred embodiment, a planar transducer is employed, the ultrasound field according to this embodiment is highly collimated, and the delivery of energy is highly localized. This allows for the coagulation of very small volumes of tissue. If larger volumes of coagulation are desired, the device can be rotated to spread the energy delivery over a larger volume. With this technique, arbitrary continuous sectors, multiple contiguous sectors, or alternatively arbitrary angular sectors of thermal coagulation can be generated. The nature of sectors generated will depend on the tissue under consideration and the location of other structures which must be avoided. The depth of coagulation at a given angular position is controlled by the choice of the ultrasound frequency delivered to tissue, and the magnitude of the power delivered. The simultaneous adjustment of these parameters which is possible with an applicator of the invention, enables

precise control over the shape of the thermal lesion parallel and transverse to the heating applicator.

In the axial direction, the type of transducer determines the amount of control offered over the heating pattern. A single element transducer has a relatively uniform field pattern along the axis (for lengths greater than 10-20 lambda); thus, the control over the axial field pattern is limited. This type of heating is suitable for the generation of large heating patterns in situations where high accuracy of the placement of thermal lesions is not required. To improve control over the heating pattern in the axial dimension, the transducer can be divided into multiple elements (greater than 6-20 wavelengths in length). These elements can be operated independently and/or simultaneously at independent powers and frequencies, thereby enabling control over the depth of coagulation along this dimension. The heating pattern can be shaped according to the tumor geometry, and three dimensional control over the shape of the thermal lesion is achieved. For the maximum amount of control, such as in situations where small volumes of tissue are targeted for ablation (cardiac ablation, neurological disorders) a phased array transducer can be implemented. The advantage of the phased array transducer is that the power distribution from the phased array transducer can be controlled, and energy can be concentrated in a focal zone away from the surface of the applicator. This can result in the rapid coagulation of volumes of tissue of the order of a few mm^3 in dimension, with well defined boundaries. In general, the delivery of maximum power away from the applicator surface also enables the generation of more uniform temperature distributions, and larger depths of coagulation. Accordingly, control over the axial depth includes at least three approaches. The first is through "steering" or direction of the focal point of an array of elements. The second is through varying frequency and/or power along the length of the applicator and, third, adjusting the applicator's actual depth in the tissue under treatment.

For the multi-element, and phased-array designs, individual elements can serve multiple functions as both high power therapy and diagnostic transducers. Ultrasound images of a treatment region can be made before or after delivery of high intensity ultrasound to localize the beam to the appropriate location, and to assess the effect of the therapy.

An MR-compatible design of the applicator makes possible the use of MR thermometry during heating, to monitor the spatial delivery of heat. Proper selection of construction materials can result in minimal imaging artefacts, and temperature measurements can be made very close to the applicator surface. The use of thermometry in conjunction with interstitial heating improves the accuracy and control over heat delivery and can identify areas of excessive/inadequate heating.

The three-dimensional appearance of a preferred heating applicator according to the invention is shown in Figure 2. The cylindrical applicator housing (2) is made of an MR compatible material such as ceramic, or metal such as brass or copper, plastics or a carbon fiber composite. The outer diameter of the applicator housing is preferably less than 5mm in size. Part of the wall of the applicator housing is removed and replaced with any means (i.e. an acoustic window) to allow ultrasound energy to propagate into tissue, for example a thin polymer film (1). The tip of the device can be blunt, rounded, or sharpened, or any other configuration depending on the method of insertion into tissue. The location of the transducer (11) is close to the end of the applicator reducing the need to insert the device beyond the target tumor, however, as is readily apparent to a person skilled in the art, the location of the transducer is not critical; it is important only that it be placed in the applicator at a position that can allow for efficient delivery of energy to the target tissue. Indeed, the transducer may move up and down the applicator and need not be fixed in any one position on the applicator. The transducer is seated on a structural support (8) within the tubing, and is sealed in place with any adhesive or fixing means including, for example epoxy (7). The electrical power to the transducer is delivered through miniature cables (5), which are

connected to the electrodes on either face of the transducer, although any means to deliver power to the transducer is within the scope of the invention. Coolant flows into the heating applicator via a port (12) located near the back of the applicator, and out from a nearby port (13). The electrical supply from an RF amplifier is connected to the heating applicator via a connector at the back end of the device (14).

A more detailed view of some structural components of an applicator according to the present invention are shown in Figure 3. The applicator housing (2) and the polymer film (1) acoustic window are depicted in Figure 3. The applicator is divided into 2 equal volumes by a wall (9) passing through the entire length of the tubing. The top volume (10) acts as the water inflow channel for transducer cooling, while the bottom volume (11) acts as the water return. The transducer (3) sits slightly elevated above the dividing wall, leaving an air space (4) to ensure the transducer is air-backed. The air space is made water-tight by means of an epoxy seal (7) around the transducer. However, any low acoustic impedance material may be used to create a low acoustic impedance interface to ensure that the direction of the propagation of the ultrasound energy generated by the transducer (3) is directed away from the low acoustic impedance interface and is thus localized. The signal wire (6) passes down the bottom volume and eventually passes through the dividing wall to connect with the transducer. The ground wire (5) passes through the top volume and is connected to the top electrode of the transducer. According to one embodiment, the entire applicator housing (2) may be metallized to provide electrical shielding of RF signals to reduce any possible interference with the MR-imaging system. However, as will be appreciated by a person skilled in the art, the entire applicator need not be metallized, i.e., only a portion thereof may be metallized.

An axial cross-sectional view is presented in Figure 4. The applicator housing (2) can be seen, along with the exposed wall covered with a polymer film (1). The dividing wall (9) can be seen extending down the length of the applicator lumen. The ground wire (5) passes down the top half

of the applicator, while the signal wire passes along the bottom half. Both wires connect to the transducer. The support steps (8) and the air space (4) below the transducer are seen in the figure. The arrows (10,11) in the figure depict the direction of water flow acting as coolant for the transducer. The front of the device is depicted with a sharp point suitable for direct penetration and insertion into tissue. Note that in this configuration the transducer is located close to the tip of the device.

Perforations or ports may be added to an applicator of the invention to inject chemotherapeutic or other drugs which are activated either thermally (e.g., heat activated liposomes) or sonically.

The possible configurations of transducer are shown in Figure 5. Each configuration has unique heating properties and capabilities. The configuration in A is called a multi-element transducer and consists of individual elements (11), greater than 6 wavelengths in the x direction. The elements are separated by an epoxy kerf (17) and there are electrodes on both surfaces of the transducer (16). In this configuration the frequency and power of each element can be controlled independently and/or simultaneously, enabling axial control over the shape of the heating pattern. Elements of this size cannot create interference patterns with each other, and therefore act as independent transducers. The configuration shown in B is a multi-element transducer called a linear array transducer. In this configuration, the elements of the transducer (16) are less than a wavelength in the x-direction, and are separated by an epoxy kerf (17). The ability to dynamically focus the ultrasound field is possible with elements of this size, and this design can be used to create a highly localized region of heating which can be steered electronically. The simplest transducer design is shown in C, called a single element transducer. The acoustic field of this transducer is dependent on the operating frequency, and there is no control over the shape of the field in the axial direction.

The device of the subject invention may have more than one of the transducers shown in Figure 5. For instance the device may have more

than one single element transducer or more than one multi-element transducer or more than one phased-array transducer. Alternatively, the device may have combinations of the transducers shown in Figure 5. In particular, the device may have three transducers wherein each transducer may be either the single element transducer, the multi-element transducer or the phased-array transducer.

The transducer(s) shown in Figures 2, 3, 4 and 5 have at least one acoustic coupling layer (not shown in those figures but shown in Figure 7 for a particular emobodiment) oriented on a surface thereof. The at least one acoustic coupling layer in combination with the transducer provides multifrequency operation of the device of the subject invention. Referring now to Figure 6, the effects of one or more acoustic matching layers on the transmission bandwidth of interstitial transducers is shown. The graph depicts the transmission efficiency, defined as the ratio of the output power to the input power, over a range of frequencies. The calculations were performed by KLM modeling of the interstitial transducers. The center frequency of the transducer was set as 6 MHz, and the matching layers were each 1/4 wavelength thick. Defining the bandwidth as the ratio of the full-width at half maximum of the curve to the center frequency (6MHz), the following results were obtained. A bandwidth of 37% is obtained with 1 acoustic matching layer; 55% with 2 acoustic matching layers, and 69% with 3 acoustic matching layers, compared with a 7% bandwidth available for a transducer with no acoustic matching layers. There is a slight reduction in the maximum efficiency as the number of acoustic matching layers is increased. However, the addition of the acoustic matching layers enables heat delivery in tissue over a wide range of frequencies at high efficiency. The ability to control the frequency of ultrasound over a wide range during heating is a simple method by which the penetration depth can be controlled.

As mentioned previously, the impedance of each acoustic matching layer is stepped down to provide a gradual change in the acoustic impedance as the ultrasound energy travels from the transducer to the tissue.

For instance, for a transducer having 3 acoustic matching layers, the transducer may have an acoustic impedance of 35, the first acoustic matching layer may have an acoustic impedance of 14, the second acoustic matching layer may have an acoustic impedance of 7 and the third acoustic matching layer may have an acoustic impedance of 2 while the tissue may have an acoustic impedance of 1.5.

The theoretical radial acoustic power distribution for a single element transducer operating at 4, 6, or 8 MHz is shown in Figure 8. The rapid drop in power with radial distance seen with the 8 MHz power distribution makes this frequency suitable for short range, rapid heating. The 4 MHz distribution is well suited for deeper heating due to the increased penetration of power. Note also that the electrical power delivery, shown in the legend of the figure, is different for each transducer. This is due to the fact that the absorption of power increases with frequency, and this must be compensated for in order to compare the power distributions equally. Based on these results, for example, a transducer with 3 acoustic coupling layers, and a center frequency of 6 MHz, would be able to deliver ultrasound energy from 4 to 8 MHz, making this kind of control over the power distribution from a single transducer possible.

A cross-sectional view of a multi-layer transducer, in combination with 3 front acoustic coupling layers, is shown in Figure 7 (although any number of acoustic coupling layers could be used). The relative size and position of the transducer elements (18), the electrode (19), and the matching layers (22-24) are shown in the figure and the inset. The acoustic coupling layers may be acoustic matching layers. Alternatively, the acoustic coupling layers may be high acoustic impedance layers or a combination of acoustic matching layers and high acoustic impedance layers as described below.

The predicted transmission spectrum for transducers in combination with a high impedance matching layer and an acoustic matching layer is shown in Figure 9. In both transducers, multiple quarter wavelength

layers of ceramics are used to create discrete passbands of high efficiency acoustic transmission. The results of Figure 9 demonstrate that appropriate choice of the layers can result in a transducer with 3 or 4 transmission bands (i.e. 3 or 4 frequencies of operation). Therefore using a combination of at least one high acoustic impedance layer and at least one acoustic matching layer with a transducer provides multifrequency operation. The value of the acoustic impedance of the high impedance acoustic layer(s) may be chosen to achieve a desired transmission spectrum since as the acoustic impedance value of the high acoustic impedance layer is increased, the transmission bandwidth starts to spread apart and become multi-peaked. For instance, as acoustic impedance is first increased, the transmission bandwidth begins to change in a fashion similar to that shown in Figure 6 as the number of acoustic matching layers was increased. Accordingly, the acoustic impedance of the high acoustic impedance layer is increased until multiple peaks having desirable bandwidth and center frequency appear in the transmission spectrum of the device.

Multifrequency operation can also be obtained with only one high acoustic impedance layer. For instance, a unique transmission bandwidth can be achieved through the application of a 1/4 wavelength layer of a material with high acoustic impedance, such as a ceramic such as PZT which has an acoustic impedance of 35. The bandwidth achieved with 1 high impedance acoustic layer is shown in Figure 10. It should be borne in mind that a high acoustic impedance material other than PZT may also be used.

KLM modeling was also used to predict the performance of transducers in combination with various front acoustic coupling layers, and experimental measurements from prototype transducers were performed to confirm predictions. In the case of 1 ceramic high acoustic impedance layer, 2 distinct frequencies of transmission are possible, one at 3.5MHz, and one at 7.5 MHz.

KLM modeling shows that even more frequencies of transmission can be created by adding additional layers of 1/4 wavelength

thick high acoustic impedance ceramic to the transducer. Calculations of the transmission bandwidth for transducers incorporating 2 ceramic high acoustic impedance layers are shown in Figure 11. The figure shows that 3 discrete bandwidths for transmission are achieved with this design of transducer. The resonant frequency of the transducer was measured to be 6.5 MHz prior to the addition of the front layers. The bandwidth of transmission at each of these frequencies is narrow, but the efficiency is high. This makes possible a single applicator with the ability to deliver ultrasound at multiple frequencies with high electrical efficiency for increased control over the depth of thermal lesion. Incidentally, the results shown in Figure 11 may also be obtained if the transducer is combined with a single 1/2 wavelength thick high acoustic impedance ceramic.

The device of the present invention preferably utilizes at least one transducer in combination with at least one high acoustic impedance layer comprising PZT to obtain the transmission spectrums shown in Figures 10 and 11. However, any high impedance acoustic material may be used as the acoustic coupling layers as long as a desirable multifrequency transmission spectrum results (i.e. the spectrum comprises sharp narrowband peaks having high efficiency and being well spaced apart in the 2 to 12 MHz frequency range).

Referring again to Figures 9 to 11, another interesting feature of having at least one high acoustic impedance layer (of suitable acoustic impedance) in the acoustic coupling layers is that the transmission spectrum of the device has peaks situated over a frequency range of 2 to 12 MHz. This is preferable since increasing the frequency of operation above 12 MHz would result in the generated ultrasound energy having an insignificant penetration depth since with increasing frequency, the depth of penetration of ultrasound energy decreases as shown in Figure 8. Furthermore, decreasing the frequency of operation below 3 MHz is not preferable since a large amount of power would have to be generated by the ultrasound transducer due to a low

absorption coefficient. Therefore, it is preferable to operate in the 2 to 12 MHz range.

Furthermore, referring more particularly to Figures 10 and 11, the use of only high acoustic impedance layers in the acoustic coupling layers provides sharper peaks (i.e. narrower) in the transmission spectrum of the device compared to the peaks shown in Figure 9. The peaks are also more spread out in frequency. The concentration of ultrasound energy in the resulting narrowband peaks also results in increased transmission efficiency which means that less heat is dissipated in the device. Furthermore, the concentration of the ultrasound in narrowband peaks and the increased spacing of the peaks in frequency allows for the more precise control of the depth of heating and the volume of the tissue that is heated.

Furthermore, referring to Figures 6 and 9 to 11, an ultrasonic device can be built having at least one transducer and three acoustic matching layers can be built wherein each transducer in combination with the three acoustic matching layers is capable of delivering ultrasound energy at high efficiency over a range of frequencies spanning approximately 70% fractional bandwidth.

Alternatively, an ultrasonic device can be built having at least one transducer and one high acoustic impedance layer of 1/4 wavelength thickness wherein each transducer in combination with the high acoustic impedance layer of 1/4 wavelength thickness is capable of delivery of acoustic energy at two discrete frequencies.

Alternatively, an ultrasonic device can be built having at least one transducer and one high acoustic impedance layer of 1/2 wavelength thickness wherein each transducer in combination with the high acoustic impedance layer of 1/2 wavelength thickness is capable of delivery of acoustic energy at three discrete frequencies.

Alternatively, an ultrasonic device can be built having at least one transducer, one high acoustic impedance layer of 1/4 wavelength

thickness and one acoustic matching layer of 1/4 wavelength thickness wherein each transducer in combination with the aforementioned layers is capable of delivery of acoustic energy at three discrete frequencies.

Alternatively, an ultrasonic device can be built having at least one transducer, two high acoustic impedance layer of 1/4 wavelength thickness and one acoustic matching layer of 1/4 wavelength thickness wherein each transducer in combination with the aforementioned layers is capable of delivery of acoustic energy at four discrete frequencies.

Alternatively, other ultrasonic devices using any combination of transducers in combination with acoustic matching layers and/or high acoustic impedance layers may be built to realize any desirable transmission spectrum having utility in the applications specified herein.

In an alternative embodiment, the piezoelectric transducer may have the acoustic coupling layer(s) oriented at the rear of the transducer as shown in Figure 12b. In a further alternative embodiment, the piezoelectric transducer may have the acoustic coupling layer(s) oriented at both the front and the rear of the transducer as shown in Figure 12c. There may be one or more acoustic coupling layers in both cases. The multiple resonances, previously discussed, should be generated regardless of whether the acoustic coupling layers are oriented at the front (i.e. Figure 12a) or the rear (i.e. Figure 12b) or at both the front and the rear (i.e. Figure 12c) of the piezoceramic transducer as long as the air interface (or other low acoustic impedance interface) remains at the same location in both orientations. For instance, in Figures 12a, 12b and 12c, the air interface occurs at the rear of the transducer. Accordingly, the direction of propagation of the ultrasound energy is away from the air interface. However, the air interface may also occur at the front of the transducer in which case the ultrasound energy would propagate away from the bottom of the transducer. Furthermore, the orientations shown in Figures 12a, 12b and 12c would be equally applicable to the single element transducer, the linear array transducer and the multi-element transducer previously described. It should also be noted that the

transducer orientation shown in Figures 12a, 12b or 12c may also be rotated a given number of degrees in a clockwise or counter-clockwise direction about the longitudinal axis of the transducer as long as appropriate components of the heating applicator that interact with the transducer are designed and oriented in a likewise fashion.

Methods Of Thermal Therapy

The envisioned technique for image-guided interstitial ultrasound coagulation of tumors in a body (i.e. a human or animal patient) is outlined in Figure 1. Alternatively, rather than inserting the device interstitially, the device may be inserted into an orifice or cavity in the body such as the anus, vagina or urethra of the patient. The device may also be inserted into a catheter which has been inserted into the patient. Prior to treatment, a 3 dimensional image data set is acquired to define the tumor volume (i.e. tissue target volume), and the surrounding anatomy of interest. Treatment planning software outlines the borders of the tumor volume, based on the acquired images. This information is then used to determine the insertion path of the transducer, the final position of the device, and a heating regime comprising selecting the scanning and operating parameters necessary to coagulate all the tissue within the treatment volume, while sparing surrounding normal tissue. The location of the device is flexible, and it can be inserted within, or adjacent to the target volume of tissue. The guidance of the device insertion is aided with rapid imaging, for example MRI, US or CT, to ensure the proper location of the device. Once the device has been inserted into the desired location in tissue, ultrasound energy is delivered and the appropriate movement and/or motion(s), frequency and/or power delivery of the applicator are undertaken. All of this therapy can be accomplished with one applicator of the invention inserted at one location. Alternatively, if other therapies are planned during the intervention, an acoustically transparent catheter can be inserted first, acting as a guide for the insertion of the heating applicator.

During treatment, images are continuously acquired to indicate the temperature distribution in the region of the applicator, for example with

MRI. This information is used to ensure adequate heating at the tumor borders, and to avoid overheating near the transducer surface. This continues until the temperature at the treatment margins exceeds a critical temperature sufficient for thermal coagulation in tissue. Once this stop-point is reached, images sensitive to thermal damage, for example T2-weighted MR images, or contrast enhance T1-weighted images, are acquired to evaluate the extent of the thermal lesion. This serves as a confirmation of the damage pattern predicted by thermometry, and further heating can be performed if necessary. If the thermal lesion covers the entire tumor volume, then the treatment is completed, and the applicator is removed. Imaging of the treatment volume after treatment can be done to follow the progress of the treated region. At this point, if a catheter was initially inserted into the tumor, other therapies/diagnosis can be executed after the removal of the heating applicator from the catheter.

Insertion of an applicator according to the present invention into tissue can be accomplished in a number of ways. The applicator can be inserted directly into the tumor volume or adjacent to the tumor volume. Alternatively, an acoustically transparent catheter can be inserted first in close proximity to the target tissue, either within or adjacent to the tumor volume. The heating applicator can then be inserted down the catheter to perform the heating. This method of insertion allows for the insertion of other devices and/or agents into the target volume for further diagnosis and treatment, such as miniature RF coils for high resolution MR imaging or spectroscopy of the treatment volume, chemotherapeutic drugs for high dose delivery to the tumor, or gene therapy vectors designed to treat the tumor.

OTHER APPLICATIONS

The applicator of the present invention can be used to deliver accurately controlled, high intensity ultrasound fields for therapy delivery mechanisms. It has been shown that ultrasound can disrupt the local blood brain barrier (Vykhodtseva et al., 1995; Patrick et al., 1990) and "sonoporate" cell membranes (Miller et al., 1999; Bao et al., 1997) which are known barriers

to some forms of drug therapy. An embodiment of the present invention could, thus, be used for various local manipulations of tissue microstructures to enhance delivery, or concentrations of therapeutic agents. Ultrasound-induced temperature elevations can also activate certain enzymes (Vekris et al., 2000) and can potentially enhance delivery mechanisms for some forms of gene therapy (Miller 2000; Lawrie et al. 1999; Kim et al., 1996). Thus, in conjunction with further biological developments, the ability to deliver accurate patterns of high intensity ultrasound could be important for targeting new therapeutic regimes.

While the present invention has been described with reference to what are presently considered to be the preferred examples, it is to be understood that the invention is not limited to the disclosed examples. To the contrary, the invention is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

All publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

FULL CITATIONS FOR REFERENCES REFERRED TO IN THE SPECIFICATION

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Claims:

1. A multifrequency ultrasonic device comprising:

a) a housing;

b) at least one transducer provided in said housing, each transducer having first and second opposed surfaces;

c) at least one acoustic coupling layer provided on at least one of said first and second surfaces of at least one of said transducers;

d) an acoustic window for transmission of ultrasound energy generated by said transducers; and,

e) means for delivering sufficient power to each transducer for generating ultrasonic energy to thermally coagulate tissue.

2. A device according to claim 1, further comprising a low acoustic impedance interface provided between said housing and at least one surface of each transducer for directing ultrasound energy generated from each transducer away from said interface.

3. A device according to claim 2, wherein said first surface of each transducer faces away from said low acoustic impedance interface.

4. A device according to claim 3, wherein said at least one acoustic coupling layer is provided on said first surface of at least one of said transducers.

5. A device according to claim 3, wherein said at least one acoustic coupling layer is provided on said second surface of at least one of said transducers.

6. A device according to claim 3, wherein said device comprises at least two acoustic coupling layers and at least one layer of said at least two acoustic coupling layers is provided on said first surface of at least one of said transducers and at least another layer of said at least two acoustic coupling

layers is provided on said second surface of said at least one of said transducers.

7. A device according to any one of claims 1 to 6, wherein at least one of said transducers is a single element transducer.

8. A device according to any one of claims 1 to 6, wherein at least one of said transducers is a multi-element transducer and said at least one acoustic coupling layer is provided on at least one of said elements.

9. A device according to claim 8, wherein each of said elements is between about 6-20 wavelengths in length.

10. A device according to any one of claims 1 to 6, wherein at least one of said transducers is a phased array transducer having a plurality of elements and said at least one acoustic coupling layer is provided on at least one of said elements.

11. A device according to claim 10, wherein each of said elements is less than about 1 wavelength in length.

12. A device according to any one of claims 7 to 11, wherein at least three transducers are incorporated into the device.

13. A device according to any one of claims 1 to 12, wherein at least one layer of said at least one acoustic coupling layer is an acoustic matching layer.

14. A device according to any one of claims 1 to 12, wherein at least one layer of said at least one acoustic coupling layer is a high acoustic impedance layer.

15. A device according to any one of claims 1 to 12, wherein said device comprises a plurality of acoustic coupling layers, at least one layer of said plurality of acoustic coupling layers is an acoustic matching layer and at

least one layer of said plurality of acoustic coupling layers is a high acoustic impedance layer.

16. A device according to any one of claims 1 to 12, wherein said device comprises three acoustic coupling layers, each of said acoustic coupling layers is an acoustic matching layer wherein each transducer in combination with said three acoustic coupling layers is capable of delivering ultrasound energy at high efficiency over a range of frequencies spanning approximately 70% fractional bandwidth.

17. A device according to any one of claims 1 to 12, wherein said device comprises one acoustic coupling layer, said acoustic coupling layer is a high acoustic impedance layer of 1/4 wavelength thickness wherein each transducer in combination with said acoustic coupling layer is capable of delivery of acoustic energy at two discrete frequencies.

18. A device according to any one of claims 1 to 12, wherein said device comprises one acoustic coupling layer, said acoustic coupling layer is a high acoustic impedance layer of 1/2 wavelength thickness wherein each transducer in combination with said acoustic coupling layer is capable of delivery of acoustic energy at three discrete frequencies.

19. A device according to any one of claims 1 to 12, wherein said device comprises two acoustic coupling layers, one of said acoustic coupling layers is a high acoustic impedance layer of 1/4 wavelength thickness and one of said acoustic coupling layers is an acoustic matching layer of 1/4 wavelength thickness wherein each transducer in combination with said two acoustic coupling layers is capable of delivery of acoustic energy at three discrete frequencies.

20. A device according to any one of claims 1 to 12, wherein said device comprises three acoustic coupling layers, two of said acoustic coupling layers are high acoustic impedance layers of 1/4 wavelength thickness and one of said acoustic coupling layers is an acoustic matching layer of 1/4

wavelength thickness wherein each transducer in combination with said three acoustic coupling layers is capable of delivery of acoustic energy at four discrete frequencies.

21. A device according to any one of claims 14, 15, 17, 18, 19, or 20, wherein each high acoustic impedance layer is made from PZT.

22. A device according to any one of claims 1 to 21, wherein the housing is made of MR-compatible materials.

23. A device according to claim 22, wherein said MR-compatible material is a metal.

24. A device according to claim 22, wherein said MR-compatible material is a ceramic.

25. A device according to claim 22, wherein said MR-compatible material is a polymer.

26. A device according to claim 23, wherein the metal is brass.

27. A device according to claim 25, wherein the polymer is poly ether ether ketone.

28. A device according to any one of claims 1 to 27, wherein said device further comprises means for controlling frequency and power of each transducer.

29. A device according to claim 28, wherein said means for controlling frequency and power of each transducer allows for the simultaneous and independent control of frequency and power.

30. A device according to claims 28 or 29, wherein said frequency is in the range of 2 to 12 MHz.

31. A device according to any one of claims 28 to 30, wherein said power is in the range of 10 to 60 Watts.

32. A device according to any one of claims 1 to 31, wherein said device further comprises a motor control system to provide rotational control of at least a portion of the housing that contains said transducers to isolate said thermal coagulation to parts of said tissue.

33. A device according to any one of claims 1 to 32, wherein said housing further comprises tube means for infusing a therapeutic agent into a patient.

34. A multifrequency ultrasonic device comprising:

a) a housing;

b) at least one transducer provided in said housing, each transducer having first and second opposed surfaces;

c) a plurality of acoustic coupling layers provided on at least one of said first and second surfaces of at least one of said transducers;

d) an acoustic window for transmission of ultrasound energy generated by said transducers; and,

e) means for providing power to each transducer.

35. A device according to claim 34, further comprising a low acoustic impedance interface provided between said housing and at least one surface of each transducer for directing ultrasound energy generated from each transducer away from said interface.

36. A device according to claim 35, wherein said first surface of each transducer faces away from said low acoustic impedance interface.

37. A device according to claim 36, wherein said plurality of acoustic coupling layers are provided on said first surface of at least one of said transducers.

38. A device according to claim 36, wherein said plurality of acoustic coupling layers are provided on said second surface of at least one of said transducers.

39. A device according to claim 36, wherein said plurality of acoustic coupling layers are provided on both said first surface and said second surface of at least one of said transducers.

40. A device according to any one of claims 34 to 39, wherein at least one of said transducers is a single element transducer.

41. A device according to any one of claims 34 to 39, wherein at least one of said transducers is a multi-element transducer and said plurality of acoustic coupling layers are provided on at least one of said elements.

42. A device according to claim 41, wherein each of said elements is between about 6-20 wavelengths in length.

43. A device according to any one of claims 34 to 39, wherein at least one of said transducers is a phased array transducer having a plurality of elements and said plurality of acoustic coupling layers are provided on at least one of said elements.

44. A device according to claim 43, wherein each of said elements is less than about 1 wavelength in length.

45. A device according to any one of claims 40 to 44, wherein at least three transducers are incorporated into the device.

46. A device according to any one of claims 34 to 45, wherein at least one layer of said plurality of acoustic coupling layers is an acoustic matching layer.

47. A device according to any one of claims 35 to 45, wherein at least one layer of said plurality of acoustic coupling layers is a high acoustic impedance layer.

48. A device according to any one of claims 34 to 45, wherein at least one layer of said plurality of acoustic coupling layers is an acoustic matching layer and at least one layer of said plurality of acoustic coupling layers is a high acoustic impedance layer.

49. A device according to any one of claims 34 to 45, wherein said device comprises three acoustic coupling layers, each of said acoustic coupling layers is an acoustic matching layer wherein each transducer in combination with said three acoustic coupling layers is capable of delivering ultrasound energy at high efficiency over a range of frequencies spanning approximately 70% fractional bandwidth.

50. A device according to any one of claims 34 to 45, wherein said device comprises one acoustic coupling layer, said acoustic coupling layer is a high acoustic impedance layer of 1/4 wavelength thickness wherein each transducer in combination with said acoustic coupling layer is capable of delivery of acoustic energy at two discrete frequencies.

51. A device according to any one of claims 34 to 45, wherein said device comprises one acoustic coupling layer, said acoustic coupling layer is a high acoustic impedance layer of 1/2 wavelength thickness wherein each transducer in combination with said acoustic coupling layer is capable of delivery of acoustic energy at three discrete frequencies.

52. A device according to any one of claims 34 to 45, wherein said device comprises two acoustic coupling layers, one of said acoustic coupling layers is a high acoustic impedance layer of 1/4 wavelength thickness and one of said acoustic coupling layers is an acoustic matching layer of 1/4 wavelength thickness wherein each transducer in combination with said two acoustic coupling layers is capable of delivery of acoustic energy at three discrete frequencies.

53. A device according to any one of claims 34 to 45, wherein said device comprises three acoustic coupling layers, two of said acoustic coupling

layers are high acoustic impedance layers of 1/4 wavelength thickness and one of said acoustic coupling layers is an acoustic matching layer of 1/4 wavelength thickness wherein each transducer in combination with said three acoustic coupling layers is capable of delivery of acoustic energy at four discrete frequencies.

54. A device according to any one of claims 47, 48, 50, 51, 52 or 53, wherein each high acoustic impedance layer is made from PZT.

55. A device according to any one of claims 34 to 54, wherein the housing is made of MR-compatible materials.

56. A device according to claim 55, wherein said MR-compatible material is a metal.

57. A device according to claim 55, wherein said MR-compatible material is a ceramic.

58. A device according to claim 55, wherein said MR-compatible material is a polymer.

59. A device according to claim 56, wherein the metal is brass.

60. A device according to claim 58, wherein the polymer is poly ether ether ketone.

61. A device according to any one of claims 34 to 60, wherein said device further comprises means for controlling frequency and power of each transducer, whereby said means for controlling frequency and power allows for adjustment of ultrasound power distribution depth.

62. A device according to claim 61, wherein said means for controlling frequency and power of each transducer allows for the simultaneous and independent control of frequency and power.

63. A device according to claims 61 or 62, wherein said frequency is in the range of 2 to 12 MHz.

64. A device according to any one of claims 60 to 63, wherein said power is in the range of 10 to 60 Watts.

65. A device according to any one of claims 34 to 64, wherein said device further comprises a motor control system to provide rotational control of at least a portion of the housing that contains said transducers to isolate ultrasound power to parts of said tissue.

66. A device according to any one of claims 34 to 65, wherein said housing further comprises tube means for infusing a therapeutic agent into a patient.

67. A multifrequency ultrasonic device comprising:

a) a housing;

b) at least one transducer provided in said housing, each transducer having first and second opposed surfaces;

c) at least one acoustic coupling layer provided on at least one of said first and second surfaces of at least one of said transducers;

d) an acoustic window for transmission of ultrasound energy generated by said transducers;

e) means for providing power to each transducer; and,

f) a motor control system to provide rotational control of at least a portion of the housing that contains said transducers to isolate ultrasound power to parts of tissue.

68. A device according to claim 67, wherein said device further comprises means for controlling frequency and power of each transducer, whereby said means for controlling frequency and power allows for adjustment of depth of said ultrasound power to parts of tissue.

69. A device according to claim 68, wherein said means for controlling frequency and power of each transducer allows for the simultaneous and independent control of frequency and power.

70. A device according to claims 68 or 69, wherein said frequency is in the range of 2 to 12 MHz.

71. A device according to any one of claims 68 to 70, wherein said power is in the range of 10 to 60 Watts.

72. A device according to any one of claims 67 to 71, further comprising a low acoustic impedance interface provided between said housing and at least one surface of each transducer for directing ultrasound energy generated from each transducer away from said interface.

73. A device according to claim 72, wherein said first surface of each transducer faces away from said low acoustic impedance interface.

74. A device according to claim 73, wherein said at least one acoustic coupling layer is provided on said first surface of at least one of said transducers.

75. A device according to claim 73, wherein said at least one acoustic coupling layer is provided on said second surface of at least one of said transducers.

76. A device according to claim 73, wherein said device comprises at least two acoustic coupling layers and at least one layer of said at least two acoustic coupling layers is provided on said first surface of at least one of said transducers and at least another layer of said at least two acoustic coupling layers is provided on said second surface of said at least one of said transducers.

77. A device according to any one of claims 67 to 76, wherein at least one of said transducers is a single element transducer.

78. A device according to any one of claims 67 to 76, wherein at least one of said transducers is a multi-element transducer and said at least one acoustic coupling layer is provided on at least one of said elements.

79. A device according to claim 78, wherein each of said elements is between about 6-20 wavelengths in length.

80. A device according to any one of claims 67 to 76, wherein at least one of said transducers is a phased array transducer having a plurality of elements and said at least one acoustic coupling layer is provided on at least one of said elements.

81. A device according to claim 80, wherein each of said elements is less than about 1 wavelength in length.

82. A device according to any one of claims 77 to 81, wherein at least three transducers are incorporated into the device.

83. A device according to any one of claims 67 to 82, wherein at least one layer of said at least one acoustic coupling layer is an acoustic matching layer.

84. A device according to any one of claims 67 to 82, wherein at least one layer of said at least one acoustic coupling layer is a high acoustic impedance layer.

85. A device according to any one of claims 67 to 82, wherein said device comprises a plurality of acoustic coupling layers, at least one layer of said plurality of acoustic coupling layers is an acoustic matching layer and at least one layer of said plurality of acoustic coupling layers is a high acoustic impedance layer.

86. A device according to any one of claims 67 to 82, wherein said device comprises three acoustic coupling layers, each of said acoustic coupling layers is an acoustic matching layer wherein each transducer in

combination with said three acoustic coupling layers is capable of delivering ultrasound energy at high efficiency over a range of frequencies spanning approximately 70% fractional bandwidth.

87. A device according to any one of claims 67 to 82, wherein said device comprises one acoustic coupling layer, said acoustic coupling layer is a high acoustic impedance layer of 1/4 wavelength thickness wherein each transducer in combination with said acoustic coupling layer is capable of delivery of acoustic energy at two discrete frequencies.

88. A device according to any one of claims 67 to 82, wherein said device comprises one acoustic coupling layer, said acoustic coupling layer is a high acoustic impedance layer of 1/2 wavelength thickness wherein each transducer in combination with said acoustic coupling layer is capable of delivery of acoustic energy at three discrete frequencies.

89. A device according to any one of claims 67 to 82, wherein said device comprises two acoustic coupling layers, one of said acoustic coupling layers is a high acoustic impedance layer of 1/4 wavelength thickness and one of said acoustic coupling layers is an acoustic matching layer of 1/4 wavelength thickness wherein each transducer in combination with said two acoustic coupling layers is capable of delivery of acoustic energy at three discrete frequencies.

90. A device according to any one of claims 67 to 82, wherein said device comprises three acoustic coupling layers, two of said acoustic coupling layers are high acoustic impedance layers of 1/4 wavelength thickness and one of said acoustic coupling layers is an acoustic matching layer of 1/4 wavelength thickness wherein each transducer in combination with said three acoustic coupling layers is capable of delivery of acoustic energy at four discrete frequencies.

91. A device according to any one of claims 84, 85, 87, 88, 89 or 90, wherein each high acoustic impedance layer is made from PZT.

92. A device according to any one of claims 67 to 91, wherein the housing is made of MR-compatible materials.

93. A device according to claim 92, wherein said MR-compatible material is a metal.

94. A device according to claim 92, wherein said MR-compatible material is a ceramic.

95. A device according to claim 92, wherein said MR-compatible material is a polymer.

96. A device according to claim 93, wherein the metal is brass.

97. A device according to claim 95, wherein the polymer is poly ether ether ketone.

98. A device according to any one of claim 67 to 97, wherein said housing comprises tube means for infusing a therapeutic agent into a patient.

99. A method for ultrasonic thermal therapy of tissue comprising:

a) determining a target tissue volume from images;

b) planning a route of insertion and a heating regime based on the images;

c) inserting a device following said route;

d) delivering ultrasonic energy from said device to said target tissue volume to produce a thermal lesion; and

e) assessing said thermal lesion with imaging.

100. A method according to claim 99, wherein step (d) further comprises monitoring temperature distribution around said device.

101. A method according to claim 99, wherein step (d) further comprises rotating at least one portion of said device to deliver heat to said target tissue volume.

102. A method according to claim 99, wherein step (d) further comprises varying the frequency of ultrasonic energy provided by said device for adjustment of the depth of heating.

103. A method according to claim 99, wherein step (d) further comprises varying the power of ultrasonic energy provided by said device for adjustment of the depth of heating.

104. A method according to claim 99, wherein step (c) comprises first inserting an acoustically transparent catheter following said route and then inserting said device into said catheter.

105. A method of delivering ultrasound for the purposes of activating a therapeutic agent in a target tissue volume to deliver therapy comprising:

a) determining the target tissue volume from images;

b) planning a route of insertion and an activation regime based on the images;

c) inserting a device following said route;

d) delivering ultrasonic energy to activate said therapeutic agent; and,

e) assessing the efficacy of activation.

106. A method according to claim 105, wherein the therapeutic agent is thermally activated.

107. A method according to claim 105, wherein the therapeutic agent is sonically activated.

108. A method according to claim 105, wherein step (d) further comprises monitoring temperature distribution around said device.

109. A method according to claim 105, wherein step (c) comprises first inserting an acoustically transparent catheter according to said route and then inserting said device into said catheter.

110. A method according to claim 105, wherein step (d) comprises first delivering said therapeutic agent using said device and then performing said delivery of ultrasonic energy.

111. A method for obtaining diagnostic information from a target tissue volume comprising:

a) determining the target tissue volume from images;

b) planning a route of insertion based on the images;

c) inserting an ultrasonic device following said route; and,

d) obtaining ultrasonic diagnostic information from said target tissue volume.

112. A method according to claims 99, 105 or 111, wherein step (a) comprises performing MR imaging.

113. A method according to claim 99, wherein step (e) comprises performing MR imaging.

114. A method according to claims 100 or 108, further comprising performing MR imaging to monitor said temperature distribution.

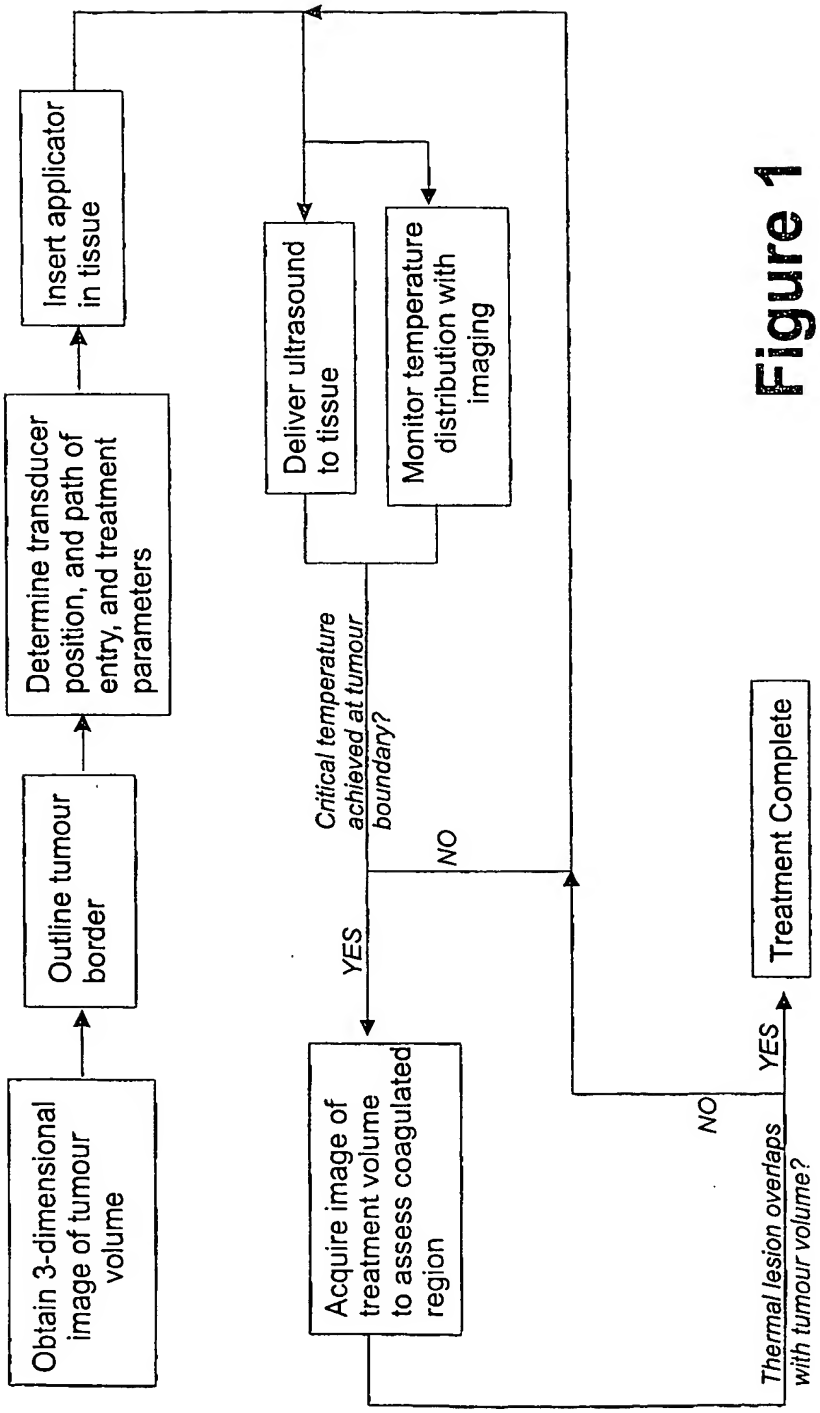

Obtain 3-dimensional image of tumour volume
Outline tumour border
Determine transducer position, and path of entry, and treatment parameters
Insert applicator in tissue
Deliver ultrasound to tissue
Monitor temperature distribution with imaging
Critical temperature achieved at tumour boundary?
YES
NO
Acquire image of treatment volume to assess coagulated region
Thermal lesion overlaps with tumour volume?
YES
NO
Treatment Complete

Figure 1

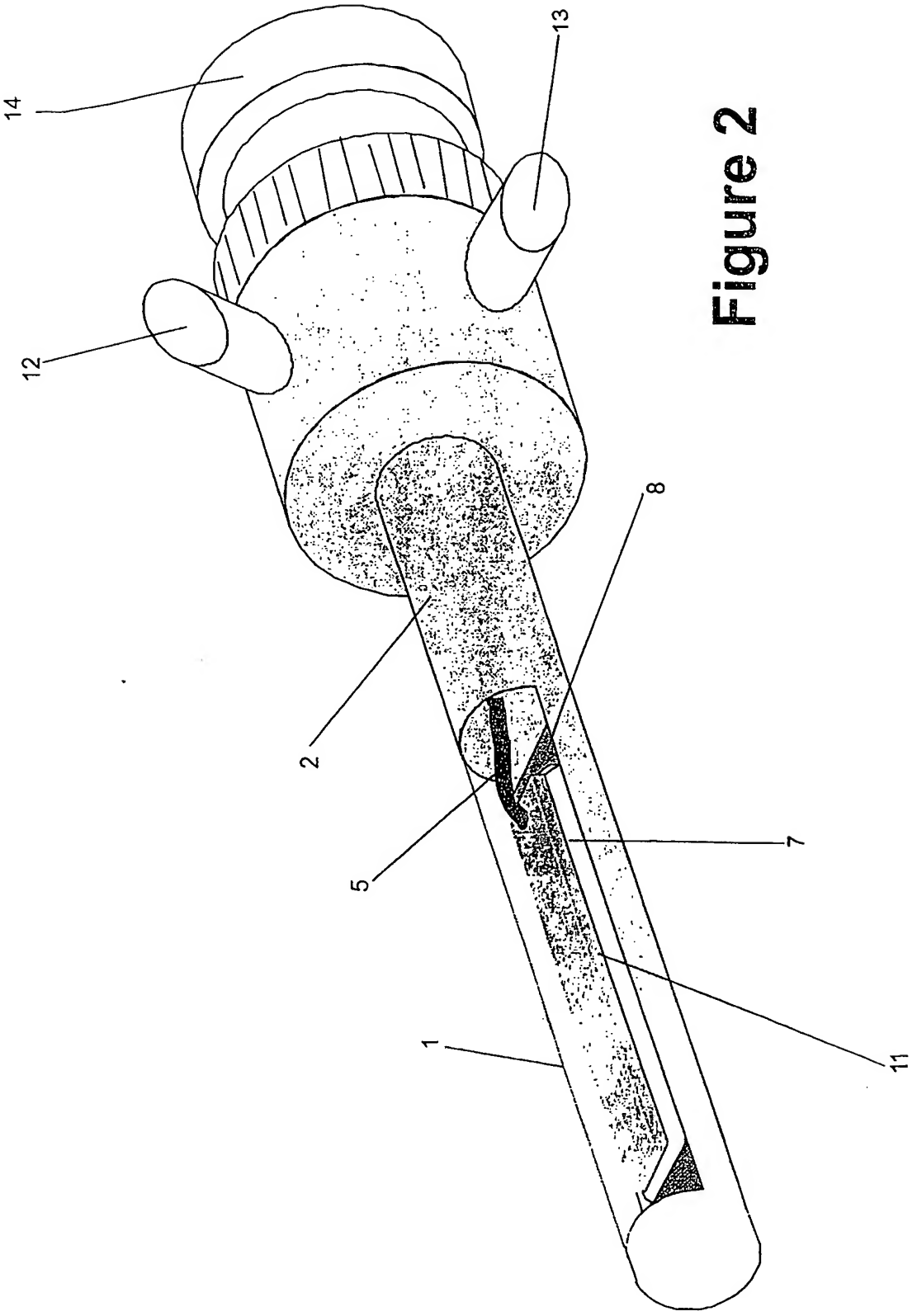
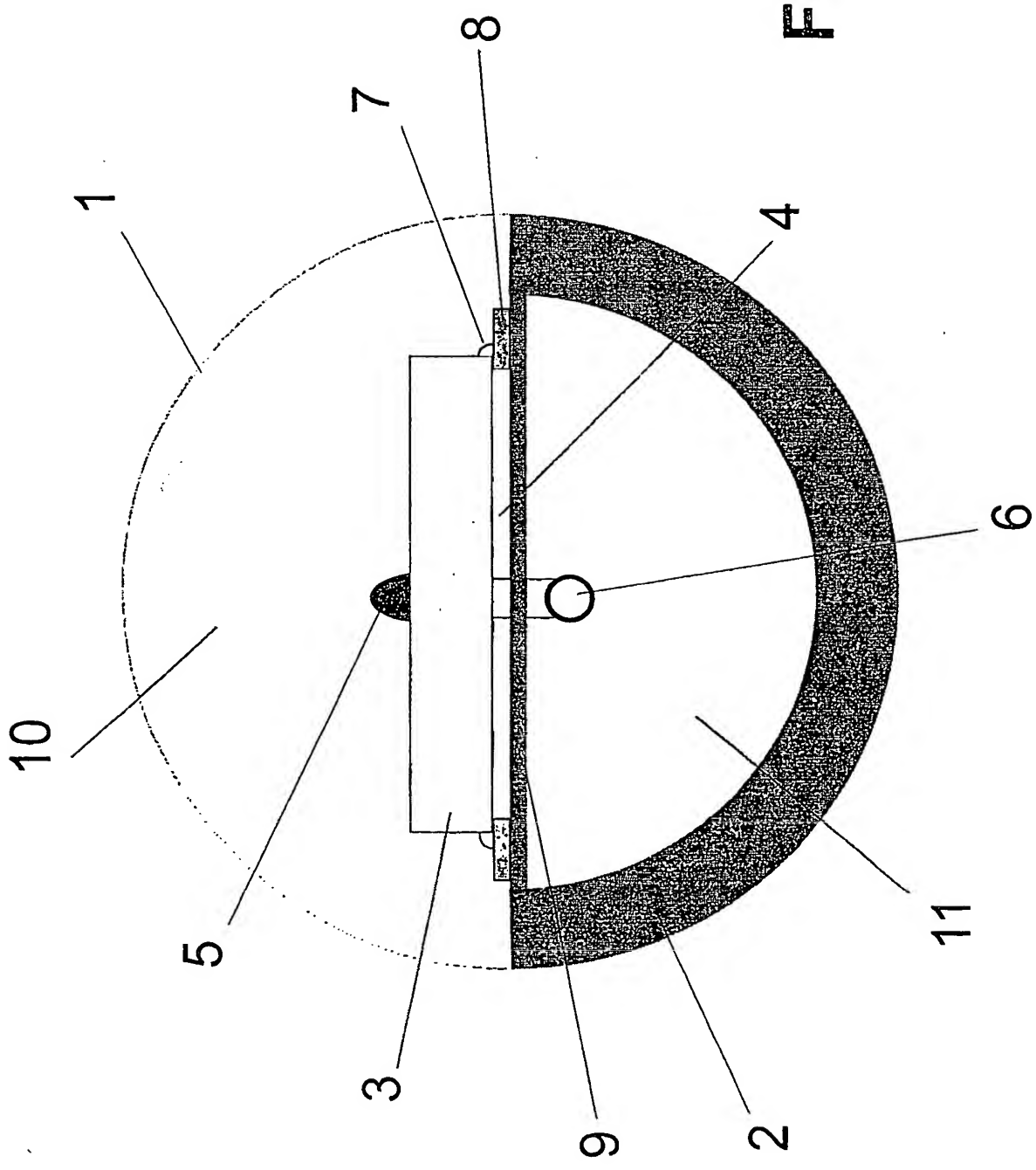


Figure 2

Figure 3



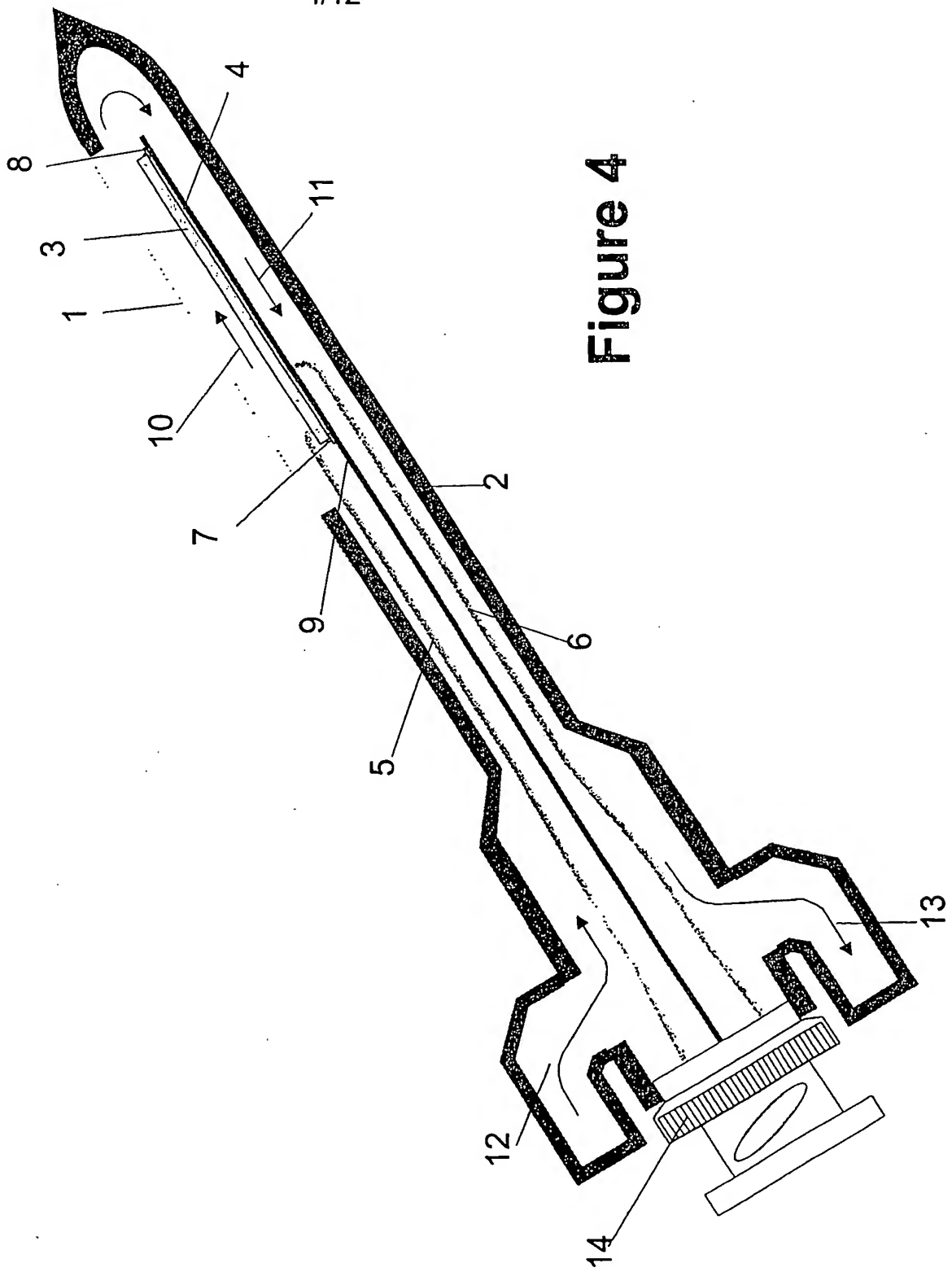


Figure 4

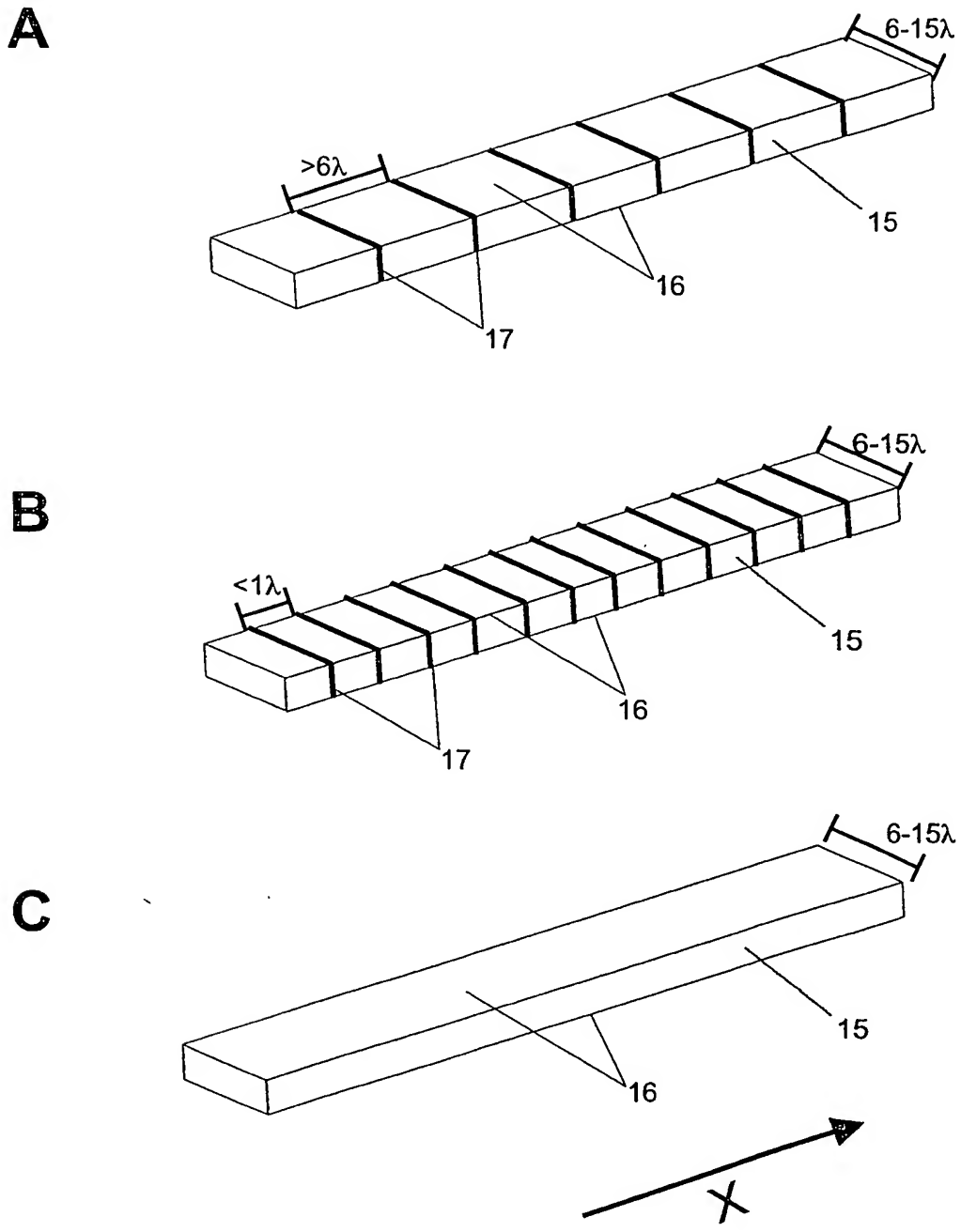


Figure 5

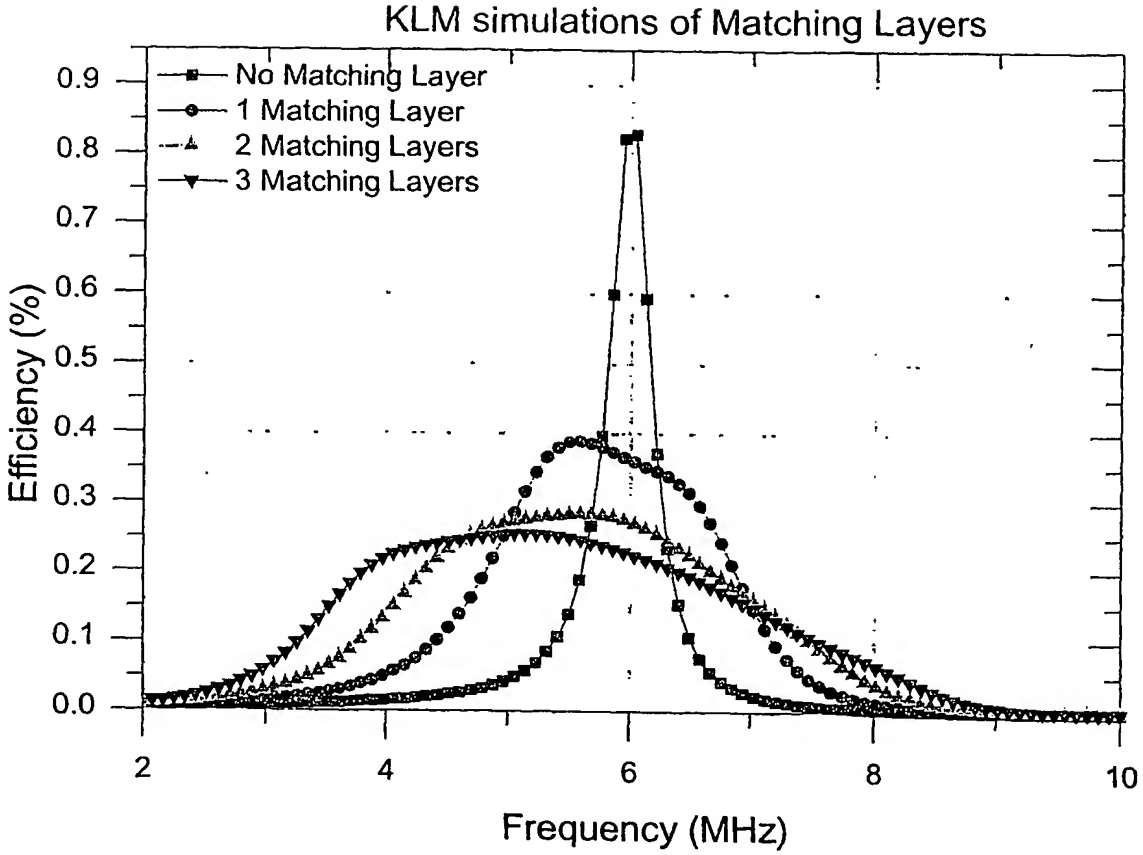

KLM simulations of Matching Layers
No Matching Layer
1 Matching Layer
2 Matching Layers
3 Matching Layers
Efficiency (%)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
2
4
6
8
10
Frequency (MHz)

Figure 6

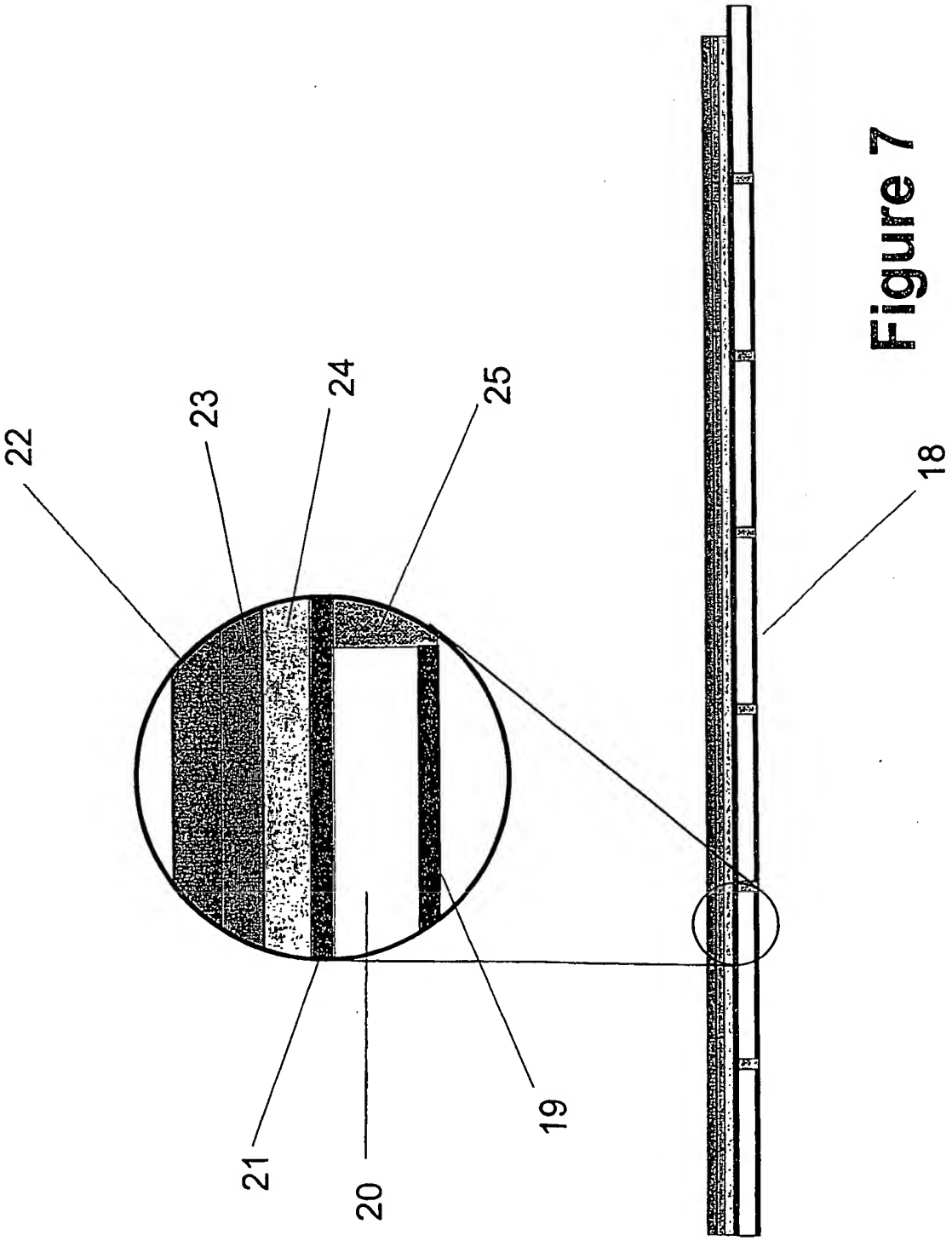


Figure 7

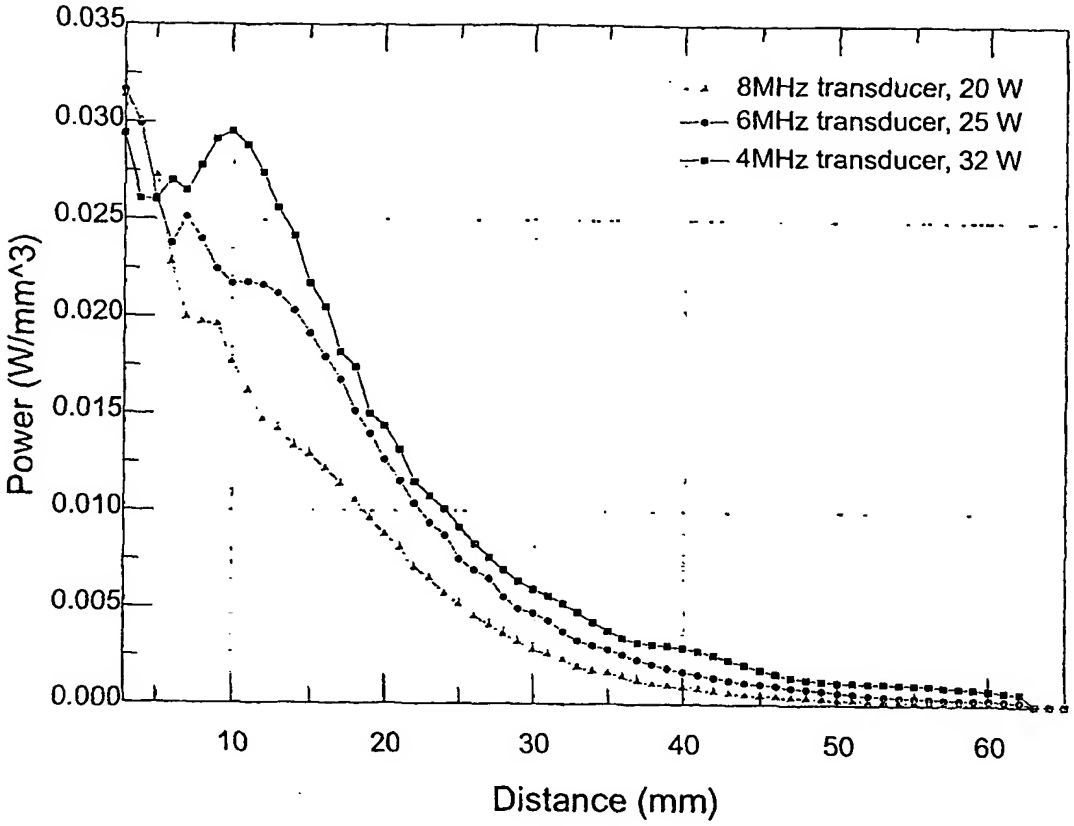

0.035
0.030
0.025
0.020
0.015
0.010
0.005
0.000
Power (W/mm^3)
10
20
30
40
50
60
Distance (mm)
8MHz transducer, 20 W
6MHz transducer, 25 W
4MHz transducer, 32 W

Figure 8

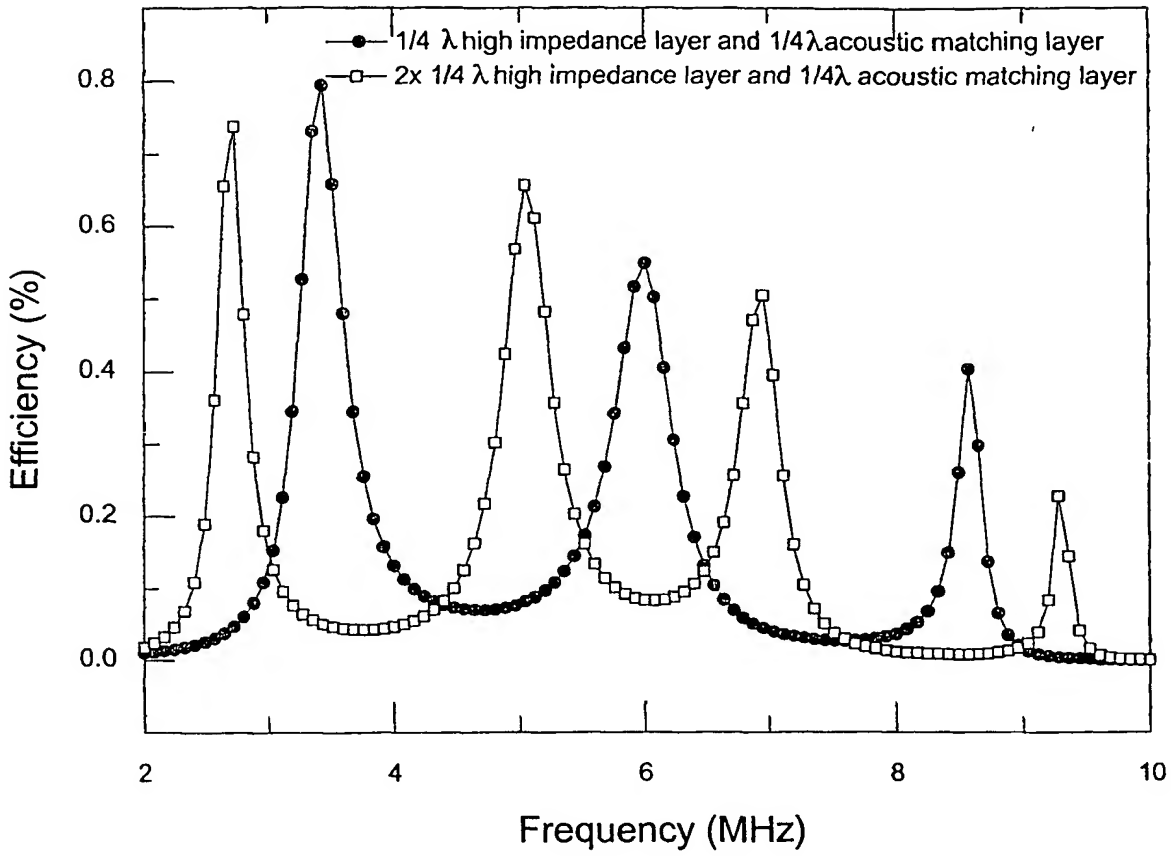

1/4 λ high impedance layer and 1/4λ acoustic matching layer
2x 1/4 λ high impedance layer and 1/4λ acoustic matching layer
Efficiency (%)
0.0
0.2
0.4
0.6
0.8
2
4
6
8
10
Frequency (MHz)

Figure 9

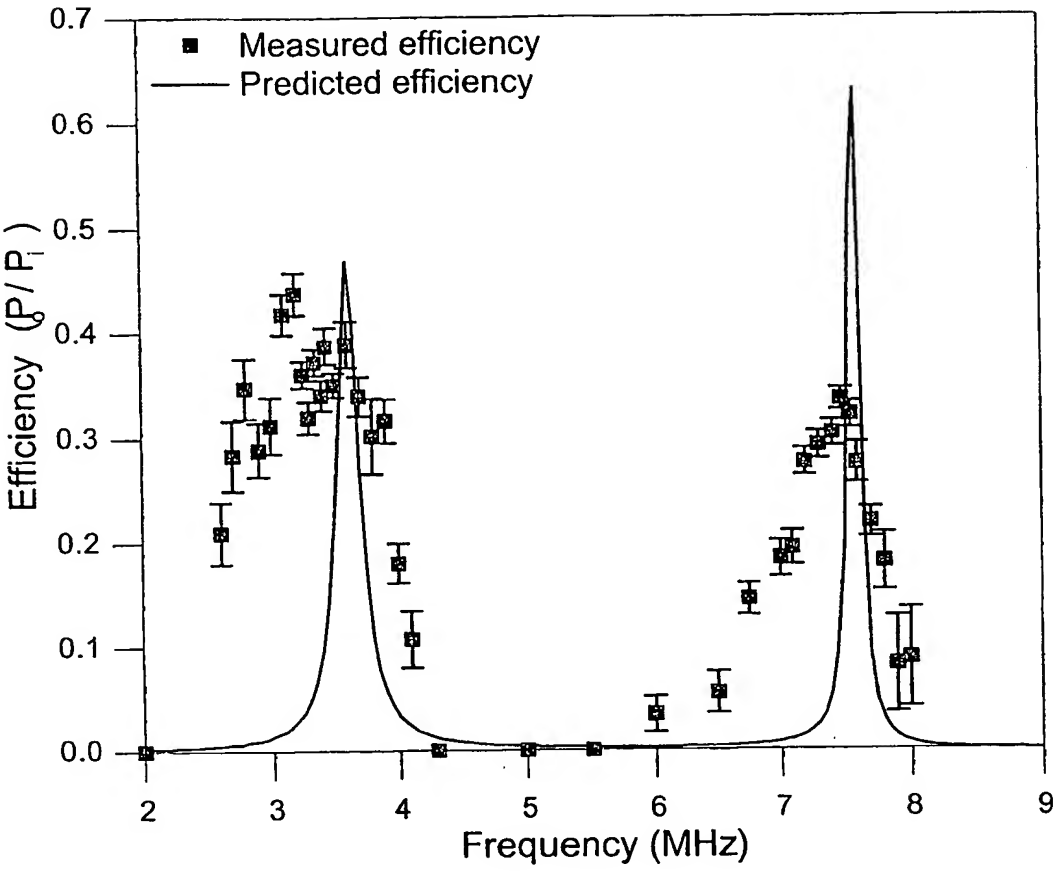

Measured efficiency
Predicted efficiency
Efficiency (P/P_i)
Frequency (MHz)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
2
3
4
5
6
7
8
9

Figure 10

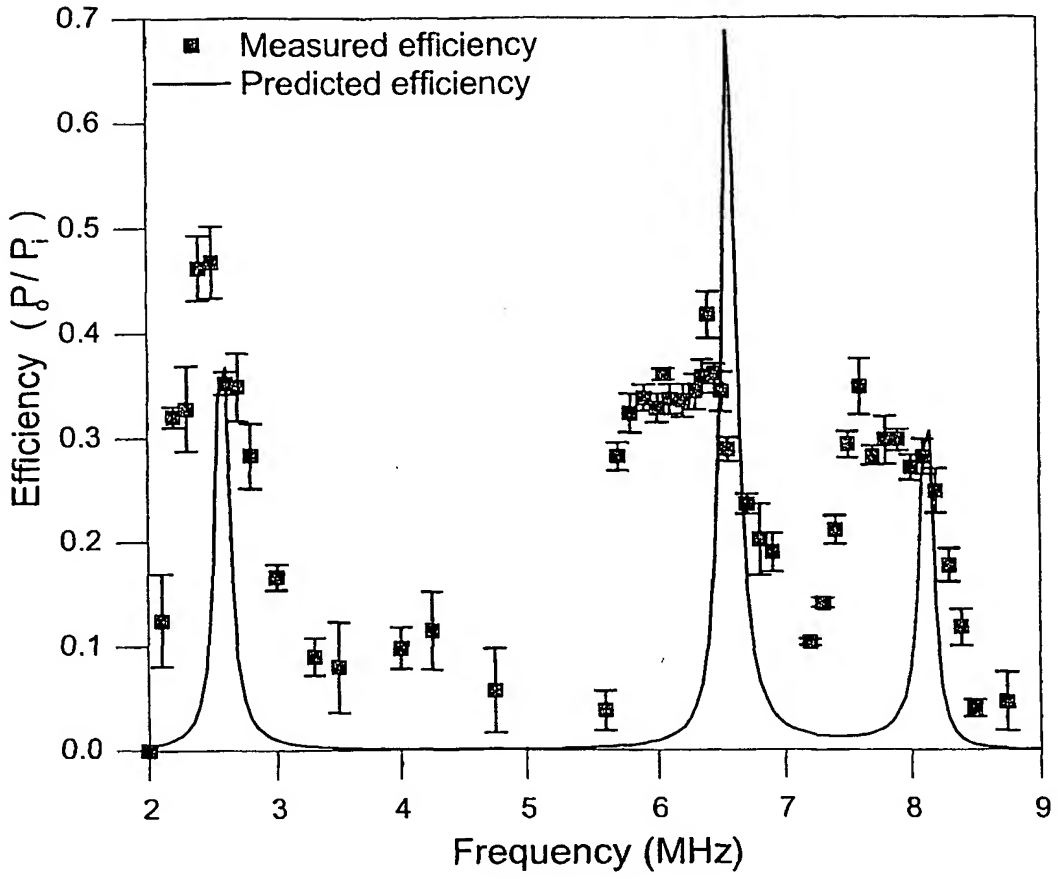

Measured efficiency
Predicted efficiency
Efficiency (P_o/P_i)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
2
3
4
5
6
7
8
9
Frequency (MHz)

Figure 11

Figure 12a

Figure 12b

Figure 12c

INTERNATIONAL SEARCH REPORT

Inte[redacted]al Application No
PCT/CA 01/01478

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61N7/02 G10K11/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61N G10K A61B B06B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, COMPENDEX

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 050 943 A (SLAYTON MICHAEL H ET AL) 18 April 2000 (2000-04-18)	1-4,7,8, 10,12, 13, 34-37, 40,41, 43,45,46
Y	column 5, line 18 - line 38 column 5, line 43 - line 45 column 5, line 59 - line 62	5,6,16, 38,39, 49,66
X	US 5 630 837 A (CROWLEY ROBERT J) 20 May 1997 (1997-05-20)	1,7,8, 10,12, 13,28, 30,31,33
Y	column 3, line 56 - line 61; figure 2	66

-/--

[X] Further documents are listed in the continuation of box C

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
8 February 2002	15/02/2002

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	page 5, line 35 - line 43; figure 3	72,73, 75,76,86
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A	column 2, line 16 - line 26	1
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			JP	9503677 T	15-04-1997
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